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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/077,719	06/08/98	NYOVIM	110223-0503

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WHITE & CASE
PATENT DEPARTMENT
1155 AVENUE OF THE AMERICAS
NEW YORK NY 10036-2787

EXAMINER	
SOLOLA, T	
ART UNIT	**PAPER NUMBER**
1626	14

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/077,718	Applicant(s) Nyqvist et al.
	Examiner Taofiq A. Solola	Group Art Unit 1626

☒ Responsive to communication(s) filed on *May 10, 2000* .

☒ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-5 and 11-20* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-5 and 11-20* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

Claim Numbering

Under the U.S. patent practice, a claim may be amended, canceled or replaced with a new claim. A claim cannot be given a new number until the application is in condition for allowance. However, a docket clerk may renumber claims to correct an apparent clerical error. Therefore, upon the receipt of the preliminary amendment filed 12/6/99, the Docket Clark in charge of this case, under Rule 126, has renumbered the new claims 18-19 as claims 19-20 respectively.

Therefore, claims 1-5, 11-20 are pending in this application.

Claims 6-10 are canceled.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 3-5, 11-14 and 19-20 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

For rejection under 35 U.S.C. 112, first paragraph, the following factors must be considered (In re Wands, 8 USPQ2d 1400, 1404 (CAFC, 1988):

1) Breadth of claims.

2) Nature of invention.

3) State of prior art.

4) Level of ordinary skill in the art.

5) Level predictability in the art.

6) Amount of direction and guidance provided by the inventor.

7) Existence of working examples.

8) Quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The breath of the claimed invention includes several species within the scope of the generic disclosure, with substituents such as, saturated and unsaturated heterocyclics which are further optionally substituted. The nature of the invention is in the field of medicinal chemistry wherein, applicants are claiming the tartrate salt of benzofuran derivatives, their use for the "prevention" of diseases listed on lines 2-4, claim 11, line 2, claim 12, line 1, claim 13, and line 2, claim 20. These diseases include, for example, thermoregulatory disturbances, sexual disturbances, disturbances of the cardiovascular system, CNS disorders and urinary incontinence. The claimed utility is not believable on its face.

The state of the prior art is what prior art knows about the nature of the invention. There is no known prior art claiming the invention of any compound for a successful "prevention" of all CNS diseases or all disturbances of the cardiovascular system.

The level of ordinary skill in the art is high but, only in the art of "treating" diseases such as sexual disturbances. The predictability or lack thereof in the art refers to the ability of one skilled in the art to extrapolate the disclosed or known results to the claimed invention. The lower the predictability, the higher the direction and guidance that must be provided by applicants. In the instant invention the predictability is very low and consequently, the need for higher levels of direction and guidance by applicants. However, applicants provide no biological assay(s) in the specification to support the claimed utility. There is no evidence in the specification that established correlation between the compound and the claimed utility. See Ex parte Mass, 9 USPQ2d 1746, 1987. The quantity of experimentation required to use the the compound as claimed in the instant invention, based on applicants nondisclosure would be undue burden because, one of ordinary skill in the art would have to perform significant amount of in-vivo experiments as well as in-vitro assays.

The term "medical disturbances" in claim 13, line 2, is not defined in the specification so as to ascertain the medical disorders that are included and/or excluded by the term. The few listed "related medical disturbances" on page 3, lines 6-8 of the specification are indicated as examples only. Therefore, it is not possible to determine the meet and bounds of the term as claimed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 3-5,12-13, and 15-19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

There is insufficient antecedent basis for the phraseology "process for the manufacture of" on line 1 of claims 15-16. Therefore, claims 15-18 are indefinite. By replacing the phraseology with "process of making" the rejection would be overcome.

The terms "CNS" in claim 13, line 1, and "5-HT_{1A}" on line 1, claims 12-13, are indefinite and therefore the claims are indefinite. A claim must stand alone to define the invention, and incorporation into the claims by reference to the specification or external source is not permitted. Ex parte Fressola, 27 USPQ 2d 1608, BdPatApp & Inter. (1993). By writing the terms in full the rejection would be overcome.

The term "substantially crystalline form" on line 2, claim 3 and lines 1-2, claim 19, is not clear as to what applicants are claiming, and therefore, claims 3-5 and 19 are indefinite. The term "substantially" implies the compound is not 100 % in crystalline form. What percentage of the salt is in crystalline form and in what form is the rest of the crystal? Applicant should note that the introduction of new subject matter into the specification will raise the issue of new matter. However, by deleting the term "substantially" the rejection would be overcome.

Applicants' arguments filed 5/10/00 have been fully considered but they are not persuasive. Applicants contend that on page 3, line 12, the specification recites "the preferred form of the salt is crystalline", and that the statement implies "noncrystalline form(s) of the salt is

also considered to be an embodiment of the invention". Applicants recite a process wherein the claimed salt is found in the amorphous form by powder X-ray diffraction ("PXRD"); and request the Examiner to make the information part of the record as a support for the noncrystalline form of the salt. Applicants further contend that they "are entitled to protection for both crystalline and noncrystalline forms of the inventive salt". This is not persuasive because applicants are entitled to only the subject matters that are disclose in the specification as originally filed. Applicant are reminded that the introduction of new subject matter into the specification will raise the issue of new matter.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-5, and 12-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Evenden et al., WO 95/11891.

Applicants claim tartaric salts of (R)-3-N,N-dicyclobutylamino-8-fluoro-3,4-dihydro-2H-1-benzopyran-5-carboxamide, their composition and method of use for the treatment of CNS disorders. Evenden et al., teach similar compounds having general formula I (page 5, lines 1-20); their organic and inorganic acids salt including salts of hydrochloric and tartaric acids (page

7, line 7), their pharmaceutical preparations (compositions) and method of use for the treatment of CNS disorders. See the abstract, page 11, lines 1-11. The difference between the instant invention and that of Evenden et al., is in the generic descriptions of the claimed compounds (salts). Therefore, the instantly claimed invention is prima facie obvious from the teaching of Evenden et al., because the indiscriminate selection of "some" among "many" is prima facie obvious. In re Lemin, 141 USPQ 814. The motivation to make the claimed compounds is to make additional compounds useful for treating CNS disorders.

Claims 15-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Evenden et al., WO 95/11891.

Applicants claim a process of making tartaric salts of (R)-3-N,N-dicyclobutylamino-8-fluoro-3,4-dihydro-2H-1-benzopyran-5-carboxamide comprising dissolving (R)-3-N,N-dicyclobutylamino-8-fluoro-3,4-dihydro-2H-1-benzopyran-5-carboxamide in an aqueous or non-aqueous organic solution of tartaric acid. Evenden et al., teach similar compounds having general formula I (page 5, lines 1-20), and a process of making their salts comprising adding ether solution of the compounds to a second ether solution of hydrochloric acid. Evenden et al., also teach that tartaric acid could be used to make the salts (page 7, line 7). The difference between the instant invention and that of Evenden et al., is in the generic descriptions of the claimed compounds (salts). Therefore, the instant invention is prima facie obvious from the teaching of Evenden et al., because the indiscriminate selection of "some" among "many" is

prima facie obvious. In re Lemin, 141 USPQ 814. The motivation is to make additional salts useful for treating CNS disorders.

Applicants' arguments filed 5/10/00 have been fully considered but they are not persuasive. Applicants contend that they have discovered a single compound from the compounds ("44") disclosed by Evenden and that they have selected only the tartrate of the salts . This is not persuasive because, as admitted by applicants, the invention by Evenden embraces the instant invention. Applicant also argue that Evenden disclosure represent a "myriad possibilities", "a multitude of compounds and a multitude of possible salts" and that the instant invention is not an indiscriminate selection of "some" among "many". This is not persuasive because, as admitted by applicants, Evenden disclose a total of "44" compounds which do not constitute a "myriad possibilities", "a multitude of compounds" or "a multitude of possible salts". Therefore, In re Ruschig, 154 USPQ 118 and In re Jones, USPQ2d 1941 are not applicable in the instant application. Applicants further argue that Evenden made no distinction between the merits of the hydrochloride and tartrate salts; that they (applicants) have found the tartrate to have superior properties over the hydrochloride; and that one of ordinary skill in the art would not have known of such superiority from the prior art by Evendel. Therefore, applicants contend that the instant application is patentable over the prior art by Evenden. This is not persuasive because the state of the art is such that one of ordinary skill in the art would know a routine procedure for making and screening the limited number of compounds (44) by Evenden so as to determine their relative activities.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Taofiq A. Solola whose telephone number is (703) 308-4690.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mr. Joseph McKane, can be reached on (703) 308-4537. The fax phone number for this Group is (703) 308-4556.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-1235.

Joseph McKane

Supervisory Patent Examiner

Group 1626

June 19, 2000